Intramural papers of the month

By Monica Frazier, Melissa Kerr, Mallikarjuna Metukuri, and Bailey Schug

A novel mechanism underlies glucocorticoid resistance

A recent study on glucocorticoid resistance, conducted by researchers at NIEHS, identified a novel mechanism that could have broad implications for various disorders, such as inflammation, autoimmune diseases, and cancer. Glucocorticoid resistance is caused by the repression of glucocorticoid receptor (GR) gene transcription by glucocorticoids. For the first time, they demonstrated that GR DNA sequences could act as a protein coding sequence in the absence of glucocorticoids, but repress the expression of the same gene in their presence.

Glucocorticoid resistance often affects patients undergoing long-term or high-dose glucocorticoid treatment for inflammatory disorders. Using both mouse and human cells, the authors have shown that binding of ligand-bound GR to a functional negative glucocorticoid response element (nGRE) in exon 6 enables assembly of a GR-NCoR1-histone deacetylase 3-containing repression complex. The assembly is mediated by chromatin looping of the intragenic elements at the transcriptional start site, thereby inhibiting transcriptional initiation.

The authors propose that GR and its ligand can coordinate the repression of GR transcription based on their concentration, irrespective of the combinatorial associations of tissue-specific transcription factors. Thus, their study suggests that long-term glucocorticoid administration may lead to constitutive repression of GR gene transcription and to glucocorticoid resistance. (**MM**)

Citation: Ramamoorthy S, Cidlowski JA. *(http://www.ncbi.nlm.nih.gov/pubmed/23428870)* 2013. Ligand-induced repression of glucocorticoid receptor gene is mediated by an NCoR1 repression complex formed by long-range chromatin interactions with intragenic glucocorticoid response elements. Mol Cell Biol 33(9):1711-1722.

COX-2 involved in the development and worsening of asthma symptoms

NIEHS scientists have discovered that the enzyme, cyclooxygenase -2 (COX-2), is responsible for regulating a specific allergic response in persons with asthma. They found that COX-2 blocks an immune cell type that gathers around the airway when an allergic reaction occurs. The immune cell, called T helper type 9 (Th9), normally fights infection, but also releases small messenger molecules that promote inflammation, which in turn, intensifies asthmatic symptoms.

The team tested the allergic response in three sets of mice — COX-2 knockout mice, normal mice given COX-2 inhibitors, and wild-type mice with fully functional COX-2. The mice were exposed to ovalbumin, the main protein in egg whites, to generate an allergic reaction, and then the team measured the Th9 cell count. The wild type mice showed low Th9 cell counts, whereas the inhibited COX-2 mice and the mice without the COX-2 gene had significantly increased numbers of Th9 cells.

The scientists were also able to replicate their findings in humans. They determined that asthmatic patients had significantly higher numbers of circulating Th9 cells, compared to their nonasthmatic counterparts. **(MK)**

Citation: Li H, Edin ML, Bradbury JA, Graves JP, Degraff LM, Gruzdev A, Cheng J, Dackor RT, Wang PM, Bortner CD, Garantziotis S, Jetten AM, Zeldin DC. *(http://www.ncbi.nlm.nih.gov/pubmed/23449692)* 2013. Cyclooxygenase-2 inhibits T helper cell type 9 differentiation during allergic lung inflammation via down-regulation of IL-17RB. Am J Respir Crit Care Med 187(8):812-822.

Early life socioeconomic factors influence the development of rheumatoid arthritis

Using data from the NIEHS Sister Study, Institute researchers have examined early life and cumulative life-course socioeconomic status (SES), and found connections with adult-onset rheumatoid arthritis (RA). This study provides additional evidence that RA may be linked with lower adult educational attainment and occupational class, and is the first to report associations of RA with younger maternal age and childhood food insecurity.

The study included 50,884 women, aged 35-74 years when they enrolled in the Sister Study, a nationwide cohort. Women were asked if a doctor had ever diagnosed them with RA, their age at diagnosis, and specific symptoms and medication use. Investigators found that several adverse childhood SES factors were more common in RA cases — young maternal age, food

insecurity, and lower parental education and household income — with a significant dose-response across an increasing number of factors. This association remained in women with lower adult educational attainment and was independent from age, race, and smoking.

The findings were consistent with a cumulative effect of lower SES throughout the lifespan. Researchers suggest that these findings support further investigation of early and sustained socioeconomic adversity. **(BS)**

Citation: Parks CG, D'Aloisio AA, DeRoo LA, Huiber K, Rider LG, Miller FW, Sandler DP. *(http://www.ncbi.nlm.nih.gov/pubmed/22586176)* 2013. Childhood socioeconomic factors and perinatal characteristics influence development of rheumatoid arthritis in adulthood. Ann Rheum Dis 72(3):350-356.

Specific DNA polymerase active site residue may influence a cell's mutagenic response to oxidative stress

NIEHS researches have determined the specific DNA minor groove interactions that modulate the DNA polymerase beta coding potential in response to the oxidative base lesion 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxoG). The current findings suggest the possibility to rationally design the polymerase to be less mutagenic after exposure to oxidative stress.

DNA lesions, which are created by reactive oxygen species after exposure to environmental stress, can lead to cancer-causing mutagenesis, if not repaired through base excision repair and other DNA repair pathways. 8-oxoG is considered the most abundant oxidative stress-induced lesion in DNA. When 8-oxoG is in the template base position during DNA synthesis, it can bind to DNA polymerase beta in two different conformations. This dual binding capacity leads to either a mutagenic (syn) pairing with the incoming adenine base, or non-mutagenic (anti) base pairing with the incoming cytosine base.

By introducing a point mutation into the polymerase active site that destabilizes the syn-conformation, the researchers were able to compare the specificity and kinetics of insertion with a templating 8-oxoG in the mutant and wild-type. They found the mutant DNA polymerase to be less error-prone than the wild-type enzyme, reflecting more frequent incorporation of cytosine opposite 8-oxoG.

The mutant polymerase structure, in complex with the 8-oxoG-containing template base and an incoming base, revealed that DNA minor groove interactions by the polymerase are necessary to stabilize the syn-conformation of 8-oxoG. Thus, the single active-site mutation changed the coding potential of the enzyme by modulating the 8-oxoG lesion conformation. **(MF)**

Citation: Freudenthal BD, Beard WA, Wilson SH. *(http://www.ncbi.nlm.nih.gov/pubmed/23267011)* 2013. DNA polymerase minor groove interactions modulate mutagenic bypass of a templating 8-oxoguanine lesion. Nucleic Acids Res 41(3):1848-1858.

View / Print PDF *(http://www.niehs.nih.gov/news/newsletter/2013/4/dir/file362468.pdf)*
(84KB)

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